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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,296	06/27/2003	**Gail Isabel Reid Adam**	11640-009-999	9001

20583 7590 10/01/2008

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
10/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/608,296	ADAM ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,38 and 40-53* is/are pending in the application.

4a) Of the above claim(s) *52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32,38,40,42-51 and 53* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/2007 has been entered.

2. Currently, claims 31, 32, 38, 40-53 are pending and under examination in the instant application.

3. Newly submitted claim 52 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 52 is directed to detection of a SNP at position 4050 or 7256 of SEQ ID NO: 1, which is structurally and functionally distinct from the SNPs under examination. Claim 52 belongs in previously submitted group V in the restriction requirement dated 3/9/2006. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 52 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

IT IS NOTED, however, that should claim 31 be amended to allowability, the restriction requirement between claim 52 and claim 31 will be withdrawn, as claim 52 depends from claim 31. Claim 52 will be rejoined and examined for patentability under 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Further, note that the prohibition against double patenting

rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

4. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non-FINAL.

Claim Rejections - 35 USC § 112

5. Claims 31-32, 38, 40, 42-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining whether a human subject is at decreased risk for fat deposition, comprising detecting the presence of an A at position of 7328 of SEQ ID NO: 1, or the presence of a T at its complementary position in a strand complementary to SEQ ID NO: 1, or a G at position 9182 of SEQ ID NO: 1, or the presence of a C at its complementary position in a strand complementary to SEQ ID NO: 1, wherein the presence of an A at position 7328, or a T at its complementary position, or a G at position 9182 of SEQ ID NO: 1, or a C at its complementary position, is indicative of a decreased risk for fat deposition, as well as a method for determining whether a human subject is at increased risk for fat deposition, comprising detecting the presence of a G at position of 7328 of SEQ ID NO: 1, or of a C at its complementary position in a strand complementary to SEQ ID

NO: 1, or a T at position 9182 of SEQ ID NO: 1, or of an A at its complementary position in a strand complementary to SEQ ID NO: 1, wherein the presence of a G at position 7328, or a C at its complementary position, or a T at position 9182 of SEQ ID NO: 1, or an A at its complementary position, is indicative of an increased risk for fat deposition, does not reasonably provide enablement for the methods as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims (31, 32, 38, 40, 42-51) encompass detecting decreased risk of fat deposition in any subject, including any mammal, by detecting the presence or absence of an A allele at position 7328 or the presence or absence of a G at position 9182 of SEQ ID NO: 1. Claim 53 encompasses detecting increased risk for fat deposition in any subject, including any mammal, by detecting the presence or absence of an A at position 7328 or a T at position 9182 of SEQ ID

NO: 1, wherein the "absence" of an A at position 7328 or the "absence" of a G at position 9182 indicates that the subject is at increased risk for fat deposition.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between the claimed polymorphisms in any subject, as well as the "absence" of a particular allele in any subject in any of the recited nucleic acids and positions and fat deposition.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 1 is the PLA2G1B nucleotide sequence. The specification teaches comparison of sequences from human PLA2G1B (SEQ ID NO: 1) and the PLA2G1B sequence from rat, mouse, and sand rat (figure 5A). The specification teaches that individuals were tested for central fat measurement and triglyceride measurements (page 41).

At page 6, the specification teaches that for "increased risk for fat deposition", individuals can be characterized as having waist/hip rations of 1.01 or more for mails and 0.91 or more for females. The specification teaches that for "leanness" or "decreased risk for fat deposition", individuals can be characterized as having waist/hip ratios of 1.00 or less for males, or 0.90 or less for females.

The specification teaches that individuals in the top and lower 10^{th} percentile were chosen as subjects and that a subset of individuals falling in the middle range were chosen as a control group. The specification teaches that potential polymorphisms in the PLA2G1B polynucleotide were identified in a publicly available SNP database and verified in a group other than the study group (page 44). The specification teaches 10 SNPs (page 44, table 1, page 49) were found to be statistically significant polymorphisms. The specification teaches that only two of these SNPs, A

at position 7328 and G at position 9182 of SEQ ID NO: 1 were found to have a statistically significant association with reduced fat deposition (leanness) (A: p=0.00669; G: p=0.00688, respectively). At page 9, the specification teaches that the presence of a G at position 7328 or a T at position 9182 are associated with central fat deposition.

The specification does not teach the presence of these alleles or the phenotypic associations in other animals. Further, the specification is silent as to whether the mere "absence of an A allele at position 7328" or "the absence of a G allele at position 9182" of SEQ ID NO: 1 are associated with increased risk for fat deposition. The specification provides no guidance as to how the SNPs at position 7328 (A) and 9182 (G) function to provide a phenotype of reduced fat deposition (leanness) or how a G at position 7328 or a T at position 9182 provide for a phenotype of increased fat deposition. The specification provides no structure/function correlation between the disclosed SNPs and increased/reduced fat deposition for the artisan to be able to predict which alleles within the claimed positions might be predictably associated with the claimed phenotypes. The two alleles: an A at position 7328 and a G at position 9128, could be part of a reduced fat deposition-associated haplotype, however the causative mutation is not necessarily one of the SNPs taught in the specification. The causative mutation could be in a gene thousands of nucleotides away, however the specification provides no indication of what this allele might be. Accordingly, the skilled artisan would not be able to predict whether the same alleles in another animal would be associated with the same phenotype, or whether the "absence" of the allele, allowing for the presence of alleles other than those actually detected, would be associated with the same phenotype. The specification provides no predictable association that any alteration at the claimed positions is associated with increased fat deposition

in humans or any other mammal. No common element or attributes of the sequences are disclosed which would permit selection of sequences as phenotypically associated polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with fat deposition is provided. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the detected reduced fat deposition may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of polymorphisms of PLA2G1B nor how their function, or lack of function, or altered function are predictably associated with fat deposition.

The state of the prior art and the predictability or unpredictability of the art:

The art does not teach the function of polymorphisms of PLA2G1B or how they are involved in fat deposition, either in humans or in non human species.

While the state of the art and level of skill in the art with regard to the detection of any known polymorphic allele is high, the level of unpredictability in associating any particular allele with a specific phenotype is even higher.

Lucentini (The Scientist; 2004, vol 24, page 20) teaches that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a

disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

Similarly, Hegele (Arterioscler. Thromb. Vasc. Biol.; 2002, Vol 22, pages 156-1061) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

As neither the art nor the specification provide guidance as to how the alterations are associated with fat deposition, the analysis required to determine in which subjects the claimed alterations are associated with a increased/ decreased fat deposition, or which alternative alleles, other than those specifically taught by the specification, are associated with fat deposition, is replete with trial and error experimentation, with the outcome of each analysis being unpredictable.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

6. Claims 31-32, 38, 40, 42-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims (31, 32, 38, 40, 42-51) encompass detecting decreased risk of fat deposition in any subject, including any mammal, by detecting the presence or absence of an A allele at position 7328 or the presence or absence of a G at position 9182 of SEQ ID NO: 1. Claim 53 encompasses detecting increased risk for fat deposition in any subject, including any mammal, by detecting the presence or absence of an A at position 7328 or a T at position 9182 of SEQ ID NO: 1, wherein the "absence" of an A at position 7328 or the "absence" of a G at position 9182 indicates that the subject is at increased risk for fat deposition.

The specification teaches that SEQ ID NO: 1 is the PLA2G1B nucleotide sequence. The specification teaches comparison of sequences from human PLA2G1B (SEQ ID NO: 1) and the PLA2G1B sequence from rat, mouse, and sand rat (figure 5A). The specification teaches that individuals were tested for central fat measurement and triglyceride measurements (page 41).

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The specification teaches that individuals in the top and lower 10^{th} percentile were chosen as subjects and that a subset of individuals falling in the middle range were chosen as a control group. The specification teaches that potential polymorphisms in the PLA2G1B polynucleotide were identified in a publicly available SNP database and verified in a group other than the study group (page 44). The specification teaches 10 SNPs (page 44, table 1, page 49) were found to be statistically significant polymorphisms. The specification teaches that only two of these SNPs, A at position 7328 and G at position 9182 of SEQ ID NO: 1 were found to have a statistically significant association with reduced fat deposition (leanness) (A: p=0.00669; G: p=0.00688, respectively). At page 9, the specification teaches that the presence of a G at position 7328 or a T at position 9182 are associated with central fat deposition.

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In analyzing whether the written description requirement is met for genus claims, it is determined whether a representative number of species have been described by their complete structure or by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. The specification only teaches an association between the specific alleles recited in the specification and the claimed phenotypes in humans. However, the genus includes non human subjects, as well as alleles which are not taught by the specification. The specification does not describe sufficiently detailed, relevant characteristics to show that applicant was in possession of the nucleic acids necessary to perform the methods as broadly claimed.

Conclusion

7. No claims are allowed. Claim 41 is objected for being dependent on a rejected claim.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday, Wednesday and Thursday from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634